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Background. **Some studies have linked low serum cholesterol levels to increased risk of colon cancer, particularly in men. Results have been inconsistent, with preclinical disease frequently offered to explain any apparent association.**

Methods. **The Framingham Study cohort of 5209 persons, initially 30–62 years of age and observed more than 30 years, was evaluated. Baseline data included lipoprotein fractions, total cholesterol levels, body mass index, alcohol intake, and cardiovascular risk variables such as cigarette smoking, hypertension, and glucose intolerance.**

Results. **In this population. colon cancer in men is related inversely to serum cholesterol levels, even when the first 10 years of follow-up are eliminated to reduce the effect of preclinical disease. This effect is concentrated in the Svedberg 0-20 fraction, corresponding to low-density lipoprotein levels. Another finding only in men is the direct relation of body mass index to colon cancer incidence.**

Conclusions. **Combined initial low serum cholesterol levels and obesity appear to indicate a four times greater risk for colon cancer in men as compared with people with average values of both variables. The reasons for these observations are unknown. *Cancer* 1992; 70:1038–1043.**

Key words: cholesterol, lipids. low-density lipoprotein, obesity, risk factors, colon cancer, epidemiology.

Since the first large cooperative drug trial to lower serum cholesterol levels indicated an apparent excess of non–cardiovascular disease mortality in the treatment group,[1] investigators have tried to determine whether low cholesterol levels confer a special risk. Much of the focus has centered on the potential relation between serum lipids and the subsequent development of malignant neoplasms, which account for a large proportion of the non–cardiovascular disease category. Many authors have found an inverse relation between initial total cholesterol level and cancer risk,[2–15] particularly that of colon cancer in men. Several studies have found the link only in the few years just before diagnosis, suggesting that the association may represent only the presence of subclinical disease.[2,11,16–18]

This report addresses the cholesterol–colorectal cancer relationship in the Framingham Study cohort, in whom baseline measurements including lipid fractions were made early and cancer incidence has been recorded for nearly 40 years later.

Methods

The Framingham Study enrolled 5209 men and women from the noninstitutionalized population of the town during 1948–1951. Initially 30–62 years of age and free of coronary disease, these people have been evaluated with biennial examinations since that time, with a loss to follow-up of less than 3%. The details of the study design, population selection, and testing and examination procedures have been published elsewhere.[19–21]

Although the Study was performed to examine the evolution of cardiovascular diseases, particularly coronary heart disease, other endpoints have been recorded as well. All subjects suspected of having had cancer have had intensive record review to confirm tissue diagnosis and/or laboratory test results, and diagnoses have been coded according to the International Classification of Diseases for Oncology, with special care to obtain the earliest date of confirmed diagnosis.[22] This analysis concerns cases with topographic codes 153 (colon—65 men and 81 women) and 154 (rectum—20 men and 22 women), found through the end of October 1988.

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Nonfasting total serum cholesterol levels were measured at examination 2 (1950–1953), with the Abell-Kendall method.[23] Lipoprotein subfractions were determined by ultracentrifugation of the same nonfasting samples, including the entire lipoprotein particle.[24] Subfractions examined include Svedberg fractions (SF) 0-20 and 20-400; SF 0-20 corresponds to low-density lipoprotein, rich in cholesterol.[25] High-density lipoprotein, not among these SF, was not measured until 18 years later and will not be incorporated in this report; however, previously published Framingham data[26] have shown no high-density lipoprotein contribution to overall cancer mortality in the relatively short follow-up period available.

In addition to the lipids, several covariates were considered to have a potential impact on the development of colorectal cancer. Body mass index was defined as weight (in kilograms) divided by the square of height (in meters). Hypertension and glucose intolerance were classified as being present or absent. Reported intake of alcoholic beverages was converted to ounces of pure ethanol and scored as weekly ingestion. Cigarettes were entered as reported number smoked per day. All of these were measured as of examination 2. Lastly, parity at examination 2 was added into the analytic model for women.

Statistical analysis consisted of proportional hazards (Cox) regression,[27] with age-stratification (blocked) of women and men into 10-year groups at baseline. Associations were examined first with the inclusion of all incident colorectal cancer cases, then excluding person-years of follow-up for the first 5 and 10 years after baseline measurements at examination 2, in an attempt to eliminate the influence of subclinical malignant neoplasms. Each of the potential risk variables was evaluated in a single risk factor model for colon cancer and rectal cancer separately. Then, multivariate models were constructed first with the total serum cholesterol along with the covariates, and then SF 0-20 with the same covariates. Finally, age-adjusted risk estimates for combined body mass index (BMI) and SF 0-20 categories were computed with the direct method.

In all analyses, strength of association is expressed as "relative hazard," referring to the hazard ratio estimated by a Cox model, approximately equivalent to the odds ratio or risk ratio. This hazard ratio per given units of change is obtained by exponentiating the Cox regression coefficient multiplied by the number of units of change (deltas). For these analyses, units of change are 20 cigarettes/day, 1 oz of pure ethanol equivalent/week, 20 mg (0.52 mmol) of total cholesterol/ml, 15 mg of SF 0-20 lipoprotein/ml, 1 kg/m^2 of BMI, yes (versus no) for glucose intolerance and hypertension, and one live birth for parity.

Results

Table 1 shows the relative hazards (and 95% confidence limits) for univariate associations with cancer of the colon and the rectum. All variables were available for 56 men and 66 women with the former and 19 men and 20 women with the latter. Because no other lipoprotein fractions showed an association with cancer incidence, only SF 0-20 appears here. Clearly, the important findings at this level appeared only in men and only for the colon: total serum cholesterol levels and SF

Table 1. Univariate Associations With Incidence of Colon and Rectal Cancer: The Framingham Study—Examination 2 Through October 1988 (Cox Regression, Stratified According to Age)

	Relative hazard (95% confidence limits) per unit of change*			
	Men		*Women*	
Risk variable	*Colon (56 cases)*	*Rectal (19 cases)*	*Colon (66 cases)*	*Rectal (20 cases)*
		1.56 (0.87–2.81)	0.68 (0.36–1.30)	
		0.99 (0.92–1.05)	0.95 (0.87–1.04)	
		0.97 (0.77–1.21)	1.05 (0.94–1.16)	
		0.98 (0.92–1.05)	1.03 (1.00–1.07)§	
		0.91 (0.80–1.05)	1.03 (0.98–1.07)	
		‖		
		1.21 (0.35–4.13)	1.10 (0.61–1.96)	1.41 (0.50–3.96)
			1.09 (0.99–1.22)	0.83 (0.65–1.07)

* Units of change are 20 cigarettes/day, 1 oz of pure ethanol equivalent/week, 20 mg (0.52 mmol) of total cholesterol/ml, 15 mg of SF 0–20 lipoprotein/ml, 1 kg/m^2 of body mass index, yes (versus no) for glucose intolerance and hypertension, and one live birth for parity.

§ $0.1 > P > 0.05$.

† $P \leq 0.05$.

‡ $P \leq 0.01$.

‖ Too few cases to assess.

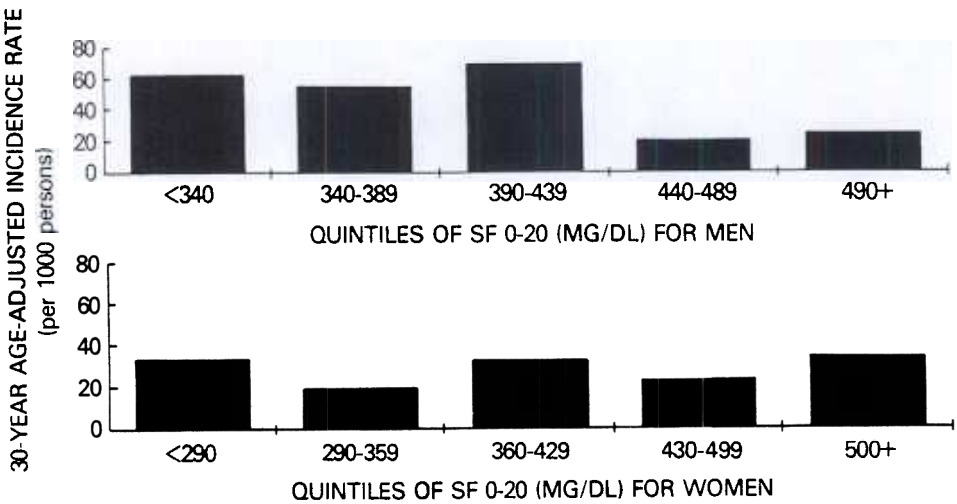

Figure 1. Relationship of baseline SF 0-20 level to 30-year incidence rate of colon cancer. Women have a wider range and lower median SF 0-20 level than men. The cancer rate drops by two-thirds for the top two quintiles for men. No trend appears for women.

0-20 related inversely to colon cancer incidence, and BMI related directly to colon cancer incidence.

To illustrate the details of the SF 0-20 relationship, in Figure 1 the baseline SF 0-20 for men and women is divided into quintiles. The age-adjusted incidence rate for colon cancer in men remains approximately level through the lower three quintiles, then decreases to a third that level for the top two. This trend is consistent across age groups (Fig. 2) and persists even when cases presenting within 10 years of baseline are excluded. Neither a trend nor a sharp decrease is seen in women. It should be observed that the numbers for the quintile ranges are appreciably higher than those expected for low-density lipoprotein–cholesterol values because SF 0-20 describes a group of lipoproteins, not just the cholesterol moiety. In fact, low-density lipoprotein–cholesterol values were not measured or calculated at examination 2. For reference purposes, however, total cholesterol quintiles for men at that time were less than 193, 193–215, 216–234, 235–259, and 260 or more mg/dl, whereas those for women were less than 190, 191–213, 214–234, 235–267, and 268 or more mg/dl.

When all of the examined variables are included in the model, the same ones again stand out. For colon cancer in men, Table 2 displays the influential variables in the multivariate analysis. The analysis was performed once with total cholesterol in the model and separately with SF 0-20 in the model instead. The value shown for BMI comes from the SF 0-20 model. Omitting person-years of follow-up for the first 5 or 10 years after baseline measurements does not dilute the relationships.

Finally, we examined this cohort to evaluate subjects with both initially low lipid values and high BMI. Figure 3 shows the association for men only, with lipids and BMI each divided into tertiles; the first 10 years of follow-up are omitted. Indeed, the combination of low SF 0-20 and high BMI carries a substantial excess risk, with a relative hazard of more than two compared with average subjects, denoted by the middle tertile for both

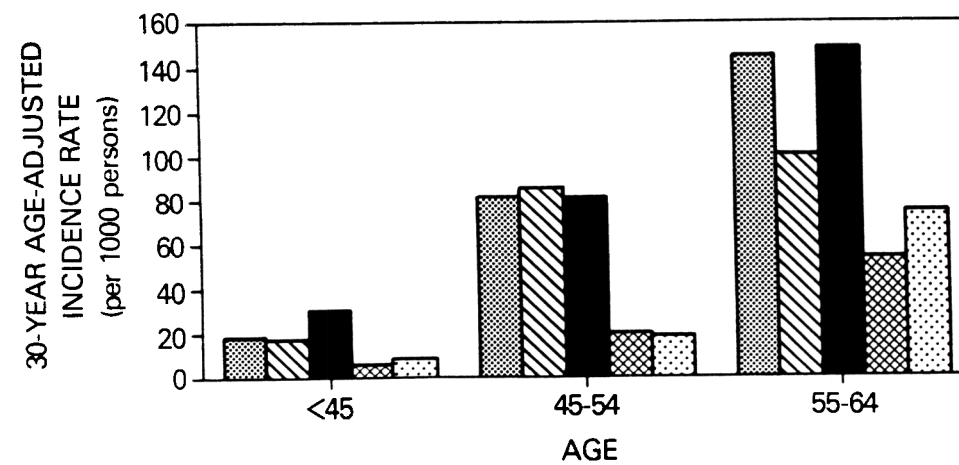

Figure 2. Relationship of baseline SF 0-20 level to 30-year incidence rate of colon cancer in men according to age at baseline. The same sharp drop in incidence among men in the top two quintiles of SF 0-20 level is seen for all age groups, attesting to the fact that it is not a phenomenon of aging. □: < 340 mg/dl, ▨: 340–389 mg/dl, ■: 390–439 mg/dl, ▩: 440–489 mg/dl, ⊠: 490 + mg/dl.

Table 2. Multivariate Associations With Incidence of Colon Cancer*: The Framingham Study of Men—Examination 2 Through October 1988 (Cox Regression Stratified According to Age)

	Relative hazard (95% confidence limits)		
	Total cholesterol	*SF 0–20*	*Body mass index*†
All cases	0.83 (0.72–0.96)‡	0.94 (0.90–0.98)§	1.09 (1.0.–1.18)‖
Omit first 5 yr of follow-up	0.84 (0.72–0.97)‖	0.94 (0.90–0.98)§	1.09 (1.00–1.18)‖
Omit first 10 yr of follow-up	0.82 (0.70–0.96)‡	0.93 (0.89–0.98)§	1.09 (1.01–1.19)‖

* Model includes cigarette smoking, alcohol consumption, serum total cholesterol or SF 0–20, body mass index, glucose intolerance, hypertension, and, for women, parity.

† Evaluated in model including SF 0–20.

‖ $P \leq 0.05$.

‡ $P \leq 0.01$.

§ $P \leq 0.005$.

variables. When total cholesterol is used in the model instead of SF 0-20, the excess risk is more than fourfold.

In men only, subsite analysis shows the same associations between total cholesterol levels, SF 0-20, BMI, and cancer development, even after 10 years, for the cecum and ascending colon but not for the rest of the colon. However, by 10 years after baseline, the total number of colon cancer cases available for analysis was 55, 27 of which were right colon lesions; and only 20 of the latter remained for multivariate analysis, making interpretations of these small numbers hazardous. Nevertheless, both in univariate and multivariate models, SF 0-20 is associated inversely with cancer incidence for both parts of the colon in men.

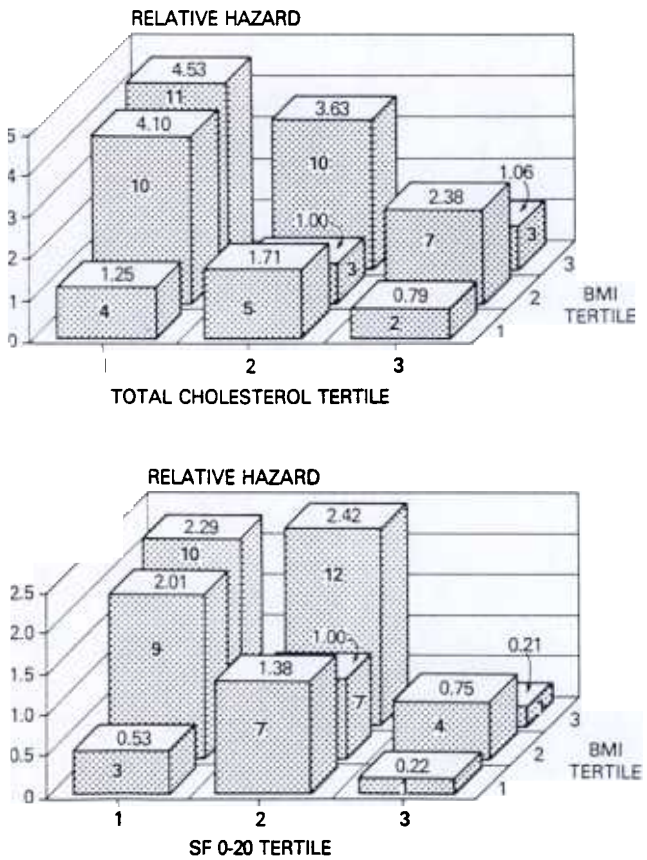

Figure 3. Combined effect of BMI and serum lipids on colon cancer incidence in men. Relative hazard (numbers atop columns) is displayed with reference to the middle tertile (the "average" man) for both BMI and either total cholesterol or low-density lipoprotein (SF 0-20). On the sides of the columns are the numbers of cases in each combined category. The first 10 years of follow-up after baseline are omitted. In all instances, the combinations of high BMI and low serum lipid signal the greatest risk.

Discussion

These results indicate an inverse relation between cholesterol level and subsequent diagnosis of colon cancer in men in the Framingham Study. Because low-density lipoprotein–cholesterol constitutes the greatest portion of total cholesterol, it is not surprising that SF 0-20 is the one fraction that seems to account for the risk, as it does to a great extent in cardiovascular disease.

The literature on the overall cholesterol–colorectal cancer relation remains inconsistent, even with respect to the subclinical disease hypothesis. The large cohort study of men screened for the Multiple Risk Factor Intervention Trial found that the inverse association between cholesterol and colon cancer mortality among those who died within 5 years after screening largely disappeared among those who died more than 5 years after screening.[11] In our study, however, it was observed that the inverse cholesterol–colorectal cancer relation among men in the Framingham Study persists even for cancers diagnosed 10 or more years after measurement of cholesterol levels.

In the many studies of the cholesterol–cancer question, the observed inverse relation tends to be found among men only. This was the case in our study as well. In the Framingham population, it is noteworthy that almost 40% of the women had SF 0-20 baseline levels in the range of the lowest quintile for the men.

The fact that BMI is related positively to colon cancer risk is not unique to this data set. Among 750,000 Americans drawn from the general population, Lew and Garfinkel have shown excess colon cancer mortality in men initially at least 40% overweight but not in women.[28] The colon cancer incidence among 8006 Japanese men living in Hawaii also has been related positively to baseline BMI.[29] However, the combination of a high BMI with low serum cholesterol levels may identify a subset of metabolically unusual people, given that, for the population as a whole, weight and cholesterol levels tend to go up and down together.[30] It remains unexplained why the low cholesterol–high BMI status confers excess colorectal cancer risk.

An apparent protective role of physical activity has been suggested to result, at least in part, from the speedier passage of potential carcinogens through the bowel.[31,32] Framingham data, based on physical activity recorded several years after the baseline of this report, indicate a protective effect only in men, unchanged after adjustment for serum cholesterol levels and BMI.[33] The inclusion of this factor in the current model did not affect the lipid–colon cancer findings.

Several recent studies have suggested a direct relation between dietary fat or total energy intake and colon cancer incidence, as well as an inverse relation with ingestion of fruit and vegetable fiber; and metabolic mechanisms have been proposed to account for these findings.[34–39] The Framingham study, however, lacks baseline dietary data, so we could not examine relations between diet and colorectal cancer or control for diet in the lipid–cancer analyses.

People with low serum cholesterol levels are likely to constitute a heterogeneous group, with some who are relatively healthy (with lifestyle-based low cholesterol levels) and some who are already ill (with disease-depressed cholesterol levels).[40] Our elimination of the first 5 and 10 person-years of follow-up is a crude epidemiologic way of accounting for preclinical cancer. This approach, however, may not fully eliminate those whose cholesterol levels are depressed either by long-incubating (more than 10 years) malignant processes or other disease conditions that might be associated with colorectal carcinogenesis.

We conclude that, in men in the Framingham study, an inverse relation exists between baseline serum cholesterol levels and the incidence of colon cancer, even after the first 10 years of follow-up are eliminated. The especially higher risk among obese people with low cholesterol levels warrants additional attention. If other investigators find similar associations to complement the results in our relatively small number of cases, it would be appropriate to work out the biologic plausibility, with consideration of dietary, metabolic, and even genetic influences.

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